



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP95/00917 (22) International Filing Date: 13 March 1995 (13.03.95) (30) Priority Data: 9404945.9 15 March 1994 (15.03.94) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): HALLWORTH, Gerald, Wynn [GB/GB]; Glaxo Research and Development Limited, Park Road, Ware, Hertfordshire SG12 0DP (GB). (74) Agents: DAWSON, Hugh, B. et al.; Glaxo plc, Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: INHALATION COMPOSITION CONTAINING LACTOSE PELLETS (57) Abstract This invention relates to a pharmaceutical composition which is suitable for the administration of medicaments by inhalation. In particular, the pharmaceutical composition comprises microfine particles of medicament and at least one lactose pellet having a diameter of from about 10 to about 1500 micrometers, which pellet comprises a plurality of microfine lactose particles. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of medicament selected from the group consisting of anti-allergics, bronchodilators, anti-inflammatory steroids and mixtures thereof in the pharmaceutical composition as defined is described also.		

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Inhalation composition containing lactose pellets

The present invention relates to an improved pharmaceutical composition, in particular a powder composition suitable for inhalation.

5 Numerous medicaments, especially those for the treatment of respiratory conditions such as asthma, are administered by inhalation. Since the drug acts directly on the target organ much smaller quantities of the active ingredient may be used, thereby minimising any potential side effects caused as a result of systemic absorption. The efficacy of this route of administration has been limited by the problems encountered in making appropriate and consistent
10 dosages available to the lungs. The delivery systems currently available are pressurised metered dose inhalers, nebulisers and dry powder inhalers.

Metered dose inhalers require good coordination of actuation and inhalation in order to achieve consistent dose administration; this coordination may be difficult for some patients. Nebulisers are effective but are relatively expensive
15 and bulky and as a result are mainly used in hospitals. A variety of dry powder inhalers have been developed and, since dry powder inhalers rely on the inspiratory effect of the patient to produce a fine cloud of drug particles, the coordination problems associated with the use of metered dose inhalers do not apply.

20 It has been found that medicaments for administration by inhalation should be of a controlled particle size in order to achieve maximum penetration into the lungs, preferably in the range of 1 to 10 micrometres in diameter. Unfortunately, powders in this particle size range, for example micronised powders, have a high bulk volume and have very poor flow characteristics due to the cohesive
25 forces between the individual particles. These characteristics create handling and metering difficulties during manufacture of the medicament powder and, most importantly, adversely affect the accurate dispensing of the powder within the inhalation device. A number of proposals have been made in the literature to improve the fluidity of dry powder pharmaceutical formulations.

30 GB1520248 describes the preparation of soft pellets of finely powdered sodium cromoglycate which have satisfactory fluidity within the reservoir of the inhaler

device but have sufficiently low internal coherence to break up into finer particles of medicament when introduced into the turbulent air stream in the mouthpiece of the device. Numerous other published patent applications suggest the use of carrier materials, for example GB1402423, particularly of coarser carriers with particles having sizes falling within a given range, for example GB1242211, GB1381872, GB1410588, GB1478020 and GB1571629. More recently WO87/05213 describes a carrier which comprises a conglomerate of one or more solid water-soluble diluents and a lubricant, EP-0260241 describes a lipid-based dry powder composition, and US5143126 describes a method of preparing flowable grain agglomerations of formoterol and lactose. Unfortunately the selection of the particle size of the drug and excipient and of the ratio of drug to excipient inevitably involves a compromise between adequate bulk and flow properties for metering and the desired redispersability of fine particle drug in the inhaled air flow.

According to the present invention there is provided a pharmaceutical powder composition suitable for inhalation which comprises microfine particles of medicament and at least one lactose pellet having a diameter of from about 10 to about 1500 micrometres, which pellet comprises a plurality of microfine lactose particles.

The particle size of the "microfine" particles of medicament and lactose should be such as to permit substantially all of the particles to be potentially available for inhalation into the lungs upon administration of the powder composition. Thus, for example, at least 90%, preferably at least 95% by weight of the particles will have a diameter of less than 15 micrometres, preferably in the range of 1 to 10 micrometres, for example 1 to 5 micrometres.

Medicaments which may be administered in the powder compositions according to the invention include any drugs usefully delivered by inhalation for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; anti-infectives, e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, e.g.

noscapine; bronchodilators, e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimeterol, salbutamol, salmeterol, terbutalin; isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament.

Particularly preferred medicaments for administration using powder compositions in accordance with the invention include anti-allergics, bronchodilators and anti-inflammatory steroids of use in the treatment of respiratory disorders such as asthma by inhalation therapy, for example cromoglycate (e.g. as the sodium salt), salbutamol (e.g. as the free base or as the sulphate salt), salmeterol (e.g. as the xinafoate salt), terbutaline (e.g. as the sulphate salt), reproterol (e.g. as the hydrochloride salt), beclomethasone dipropionate (e.g. as the monohydrate), fluticasone propionate or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol. Salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof are especially preferred.

It will be appreciated by those skilled in the art that the powder compositions according to the invention may, if desired, contain a combination of two or more active ingredients. Medicaments may be selected from suitable combinations of the medicaments mentioned hereinbefore. Thus, suitable combinations of bronchodilatory agents include ephedrine and theophylline, fenoterol and ipratropium, and isoetharine and phenylephrine formulations.

Other powder compositions may contain bronchodilators such as salbutamol (e.g. as the free base or as the sulphate salt), salmeterol (e.g. as the xinafoate

salt) or isoprenaline in combination with an antiinflammatory steroid such as a beclomethasone ester (e.g. the dipropionate) or a fluticasone ester (e.g. the propionate) or a bronchodilator in combination with an antiallergic such as cromoglycate (e.g. the sodium salt). Combinations of isoprenaline and sodium cromoglycate, salmeterol and fluticasone propionate, or salbutamol and beclomethasone dipropionate as especially preferred.

The final powder composition desirably contains 0.1 to 90% w/w, preferably 0.5 to 75% w/w, especially 1-50% w/w, of medicament relative to the weight of the lactose pellets.

The internal strength or coherence of the lactose pellets of use in the present invention may be high ("hard" lactose pellets) or low ("soft" lactose pellets) or a mixture of "hard" and "soft" pellets. However, a preferred embodiment of the invention contains "soft" lactose pellets with a low internal coherence. These lactose pellets are friable and have an internal coherence such that the pellets remain substantially intact under conditions of packaging, transport, storage and when fluidised within a container in the inhalation device from which it is intended to dispense the composition according to the invention e.g. unit dose container or bulk reservoir and yet may be disrupted into independent microfine lactose particles upon egress into the turbulent air stream within the mouthpiece of the inhaler device. The coherence or strength of the pellets may be determined by methods known to those skilled in the art, for example by a simple strength test such as that described in GB1520247. Preferred lactose pellets have a crushing weight of between 50 and 500mg, preferably between 50 and 200mg, especially between 50 and 100mg, when measured in accordance with the crushing test described herein.

The lactose pellets optionally contain one or more conventional pharmaceutically acceptable ingredients such as diluents, binders, solvents, surfactants, colouring and flavouring agents. However, the lactose pellets preferably consist essentially of microfine lactose particles.

The lactose pellets may be prepared by dry or wet pelleting methods known in the art. Thus, for example, microfine lactose particles may be dry pelleted using a tumbling or agitation process known as "balling", for example as described in

US5143126. Alternatively, microfine lactose particles may be wet pelleted by tumbling in a container together with a minimal amount of liquid (see for example, review by C. Orr (1966), Particulate Technology, Chapter 9, published McMillan, New York). Suitable liquids wet the lactose particles adequately without dissolving them and have a sufficiently low boiling point to ensure rapid evaporation from the pellets thus formed and may be selected from, for example, alkanes, halogenated alkanes, alcohols, esters and ethers. Suitable liquids include, for example cyclohexane, n-hexane, chloroform, methylene chloride, CFC-113, methanol, ethanol, isopropanol, ethyl acetate and acetone and mixtures thereof. Lactose pellets may also be prepared, for example by controlled agglomeration in a fluidised bed or by spray drying a slurry of the lactose particles.

The preparation and storage of lactose pellets is desirably carried out under anhydrous conditions to obviate any adverse effects of free moisture on the strength of the lactose pellets. Lactose is generally utilised in the form of its monohydrate, which solvate contains approximately 5% w/w bound water. Desirably, the lactose pellets are substantially free of unbound water (free moisture), for example containing less than 1%, particularly less than 0.1% by weight of unbound water. The use of anhydrous lactose particles may be preferred.

Once formed, the lactose pellets may be admixed with microfine particles of one or more medicaments, optionally together with one or more conventional pharmaceutically acceptable ingredients, using conventional techniques to prepare the powder compositions according to the invention.

In one preferred embodiment of the invention the microfine medicament particles are coated onto the lactose pellets while tumbling, either as a fine powder, liquid suspension or solution of medicament. Coating with a liquid suspension of medicament particles by a process known as "layering" is preferred. Thus, the lactose pellets may be tumbled with a dispersion of microfine medicament particles in a suitable low boiling point, non-solubilising liquid, such as an alkane, halogenated alkane, alcohol, ester or ether. Suitable liquids will vary according to the medicament used but may include, for

example, cyclohexane, n-hexane, chloroform, methylene chloride, CFC-113, methanol, ethanol, isopropanol, ethyl acetate and acetone and mixtures thereof.

Suitably a low wetting volume, for example 0.6:1 v/w liquid : medicament powder is employed in the layering process to prepare coated pellets. However, such concentrated suspensions of certain medicament and liquid combinations may be too viscous to be layered in this manner and it may be necessary and/or desirable to prepare coated pellets by continuous or intermittent spraying of a more dilute medicament suspension onto the lactose pellets under conditions of controlled evaporation. Alternatively, the lactose pellets may be slurried or sprayed with a suspension of medicament in a suitable non-solubilising liquid, followed by evaporation of the liquid to provide medicament-coated lactose pellets.

For all layering processes it is desirable to restrict the size range of the core pellets and hence it may be advantageous to pass the lactose pellets through one or more sieves to remove over or under-size pellets before layering with medicament. Desirably the lactose pellets have a diameter within the range of 50 to 1000 micrometres, particularly 150 to 1000 micrometres, for example in the range of 200 to 800 micrometres.

In an alternative embodiment the micronised medicament particles may be pelleted by methods known or analogous to methods known in the art. After pelleting, the medicament pellets may be admixed with the lactose pellets to provide a powder composition according to the invention which comprises at least one medicament pellet comprising a plurality of microfine medicament particles and at least one lactose pellet comprising a plurality of microfine lactose particles, each of said pellets having a diameter of from about 50 to about 1500 micrometres.

The powder compositions according to the invention optionally contain one or more conventional pharmaceutically acceptable ingredients such as diluents and flavouring agents. The particle size of any such ingredients will preferably be such as to substantially prevent their inhalation into the bronchial system upon administration of the powder composition, desirably in the range of 50 to 1000 micrometres.

The final powder composition desirably contains 0.1 to 90% w/w, preferably 1 to 20% w/w of medicament and 10 to 99.9% w/w, preferably 50 to 99% w/w of lactose pellets.

5 It is important that the powder compositions according to the invention are manufactured, packed and stored under substantially anhydrous conditions. Preferably the powder compositions contain less than 1%, especially less than 0.1% w/w of unbound water.

10 The compositions according to the invention may conveniently be filled into a bulk storage container, such as a multi-dose reservoir, or into unit dose containers such as capsules, cartridges or blister packs, which may be used with an appropriate inhalation device, for example as described in GB2041763, WO91/13646, GB1561835, GB2064336, GB2129691 or GB2246299. Such inhalers which contain a composition according to the invention are novel and form a further aspect of the invention. The compositions of the invention are particularly suitable for use with multi-dose reservoir-type inhaler devices in which the composition is metered e.g. by volume from a bulk powder container into dose-metering cavities. The lower limit of powder delivery which may be accurately metered from a multi-dose reservoir-type inhaler device is in the region of 100 to 200 micrograms. The formulations of the present invention are therefore particularly advantageous for highly potent and hence low dose medicaments which require a high ratio of excipient for use in a multi-dose reservoir-type inhaler device.

25 Dry powder inhalers are designed to deliver a fixed unit dosage of medicament per actuation, for example in the range of 10 to 5000 micrograms medicament per actuation, preferably 25 to 500 micrograms.

30 Administration of medicament may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment. It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular medicament used and the frequency of administration and will ultimately be at the discretion of the attendant physician. When combinations of medicament are employed the dose of each component of the combination will in general be that employed for each

component when used alone. Typically, administration may be one or more times, for example from 1 to 8 times per day, giving for example 1,2,3 or 4 unit doses each time.

Thus, for example, each actuation may deliver 25 micrograms salmeterol, 100
5 micrograms salbutamol, 25, 50, 125 or 250 micrograms fluticasone propionate or 50, 100, 200 or 250 micrograms beclomethasone dipropionate.

Crushing Test

A number of tests for the friability (strength or internal coherence) of pellets or granules have been described in the literature, see for example GB1520247
10 and Ganderton & Hunter (1971), J.Pharm.Pharmacol 23, Suppl. 1S-10S, and instrumentation specifically devised for this purpose is now available, for example from Etewe GmbH, Karlsruhe. A simple method was devised and used to assess the crushing weight of pellets according to the invention.

Thus, a single pellet was placed on a marked centre position on a base slide
15 and viewed from above through a stereomicroscope. Microscopy glass coverslips were used as weights, either 22mm square (mean 170mg, SD 4mg) or 16mm circular (mean 75mg, SD 4mg). The first weight was supported at one side and released by sliding the support away laterally. Any free-fall was minimised by standardising the pellet diameter. When a single weight did not
20 fracture or crush the pellet, further weights were applied sequentially.

Weak pellets characteristically showed crushing of the upper surface and a sharp diametric break, at mean crushing weights of less than 500mg, preferably less than 250mg.

The invention is illustrated by the following examples.

25 Example 1 - Lactose pellets

Micronised lactose monohydrate (2g) was placed in a tubular glass screw-cap scintillation vial and acetone (1.2ml) was applied to the headspace walls to avoid localised overwetting. The vial was capped immediately and rotated by hand at 45° to the vertical to give suitable powder flow to induce balling. An
30 occasional sharp tap on the bench was needed to dislodge powder adhering to

the vial or forming large agglomerates. As soon as all free powder had disappeared the pellets were immediately stored over silica gel.

Example 2 - Lactose pellets

5 Micronised lactose monohydrate (50g) was placed in a cylindrical glass pelletising pan of 160mm diameter and 80mm depth, tapering towards entry, with an axial driving spindle mounted on the flat base. The pan was mounted in the driving chuck of an electric motor at 45° to the vertical and run at 30 rpm (peripheral angular velocity = 0.25ms^{-1}). This arrangement gave the required flow pattern in which the powder climbed and then flowed down over a wide
10 region of the flat base of the pan. A coarse liquid spray of CFC-113 (30ml) was generated with a "Polyspray 2" (Hozelock) spray gun after pressurising the tank initially with 60 actuations of the hand air pump. The pellets were tumbled for 5 minutes in the closed pan and then immediately stored over silica gel.

Example 3 - Coated lactose pellets

15 Lactose pellets prepared according to Example 2 were sieved through stainless steel sieves to provide a fraction of pellet size 355-500 μm . Sieved lactose pellets (2g) were mixed with micronised salmeterol xinafoate (100mg) and then the mixture was placed in a scintillation vial. CFC-113 (60 μl) was applied to the headspace walls, the mixture tumbled as described in Example 1, air dried for 2
20 minutes and the pellets were immediately stored over silica gel. The oversize fractions (>500 μm) were removed by sieving.

The drug was determined to be uniformly distributed and the layered pellets were weak as required and gave good respirable drug delivery i.e. redispersion when tested e.g. for delivery from a Turbohaler inhalation device as measured
25 by the twin impinger assay. As used herein reference to the "twin impinger assay" means "Determination of the deposition of the emitted dose in pressurised inhalations using Apparatus A" as defined in British Pharmacopoeia 1988, pages A204-207, Appendix XVIIC.

Examples 4 to 6 - Lactose pellets

Lactose pellets were prepared as described in Example 1 using either cyclohexane, acetone or CFC-113: absolute ethanol (50:50 v/v) in place of CFC-113.

5 Example 7 - Lactose pellets

Micronised lactose monohydrate (approx 5g) was shaken by hand over a 710 μ m aperture sieve to produce friable lactose pellets.

Example 8 - Lactose pellets

10 Micronised lactose monohydrate (1g) was tumbled in a rotating glass vial for 20 minutes to produce friable lactose pellets (42% in sieve range 250-710 μ m).

CLAIMS

1. A pharmaceutical powder composition suitable for inhalation comprising microfine particles of medicament and at least one lactose pellet having a diameter of from about 10 to about 1500 micrometers, which pellet comprises a plurality of microfine lactose particles.
2. A pharmaceutical powder composition according to claim 1, wherein said at least one lactose pellet has a diameter of from about 150 to 1000 micrometers.
3. A pharmaceutical powder composition according to claim 1 or claim 2, wherein at least about 90% by weight of the microfine particles of lactose have a diameter of less than about 15 micrometers.
4. A pharmaceutical powder composition according to any preceding claim, wherein said at least one lactose pellet is hard or soft.
5. A pharmaceutical powder composition according to claim 4, wherein the soft lactose pellet has a crushing weight of about 50 to about 500mg as determined by the crushing test described herein.
6. A pharmaceutical powder composition according to claim 5, wherein the soft lactose pellet has a crushing weight of about 50 to about 100mg as determined by the crushing test described herein.
7. A pharmaceutical powder composition according to any preceding claim, wherein the medicament is selected from the group consisting of anti-allergies, bronchodilators, anti-inflammatory steroids and mixtures thereof.
8. A pharmaceutical powder composition according to claim 7, wherein the medicament is salmeterol xinafoate.
9. A pharmaceutical powder composition according to claim 7, wherein the medicament is salbutamol sulphate.

10. A pharmaceutical powder composition according to claim 7, wherein the medicament is fluticasone propionate.
- 5 11. A pharmaceutical powder composition according to claim 7, wherein the medicament is beclomethasone dipropionate or a physiologically acceptable solvate thereof.
12. A pharmaceutical composition according to any preceding claim, wherein the microfine particles of medicament form at least one medicament pellet.
- 10 13. A process for preparing a pharmaceutical composition according to any preceding claim, comprising admixing microfine particles of medicament with at least one lactose pellet having a diameter of from about 10 to about 1500 micrometers, which pellet comprises a plurality of microfine lactose particles.
- 15 14. A process according to claim 13, wherein the admixing comprises coating the lactose pellets with a liquid suspension or solution of medicament.
- 20 15. An inhalation device comprising a compound according to any one of claims 1 to 12.
- 25 16. A composition according to any one of claims 1 to 12, wherein the medicament is selected from the group consisting of anti-allergics, bronchodilators, anti-inflammatory steroids and mixtures thereof, for use in the treatment of respiratory disorders.
- 30 17. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a pharmaceutical powder composition which comprises microfine particles of medicament selected from the group consisting of anti-allergics, bronchodilators, anti-inflammatory steroids and mixtures thereof and at least one lactose pellet having a diameter of from about 10 to about 1500 micrometers, which pellet comprises a plurality of microfine lactose particles.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/00917

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,87 05213 (CHIESI FARMACEUTICI) 11 September 1987 cited in the application see claims 1-3,8-12 -----	1-7,9, 11-13, 15-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

3 July 1995

Date of mailing of the international search report

7.5

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 95/00917

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 17 is directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/00917

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8705213	11-09-87	AU-B- 597964	14-06-90
		CA-A- 1297012	10-03-92
		DE-D- 3787502	28-10-93
		DE-T- 3787502	20-01-94
		EP-A,B 0239798	07-10-87
		EP-A,B 0258356	09-03-88
		JP-T- 63502895	27-10-88
		ZA-A- 8701523	24-08-87
